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Comparison of topical glyceryl trinitrate with lignocaine ointment for treatment of anal fissure: A randomised controlled trial

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ABSTRACT

Introduction: Topical glyceryl trinitrate (GTN) has gained popularity as a treatment for anal fissure in the West. In our country, lignocaine is still the current treatment for the entity. This study was done to compare the effect of GTN with lignocaine in terms of healing rate and recurrence in South Asian population.

Methods: A prospective, double blinded, randomised controlled trial was conducted on 50 patients (both treatment arms included) of all ages and either gender with a clinical diagnosis of anal fissure. Group A was given 0.2% GTN ointment and Group B was given lignocaine ointment. Both subjective and objective signs of healing were assessed and adverse effects of the treatment were sought.

Results: Symptomatic relief was earlier with GTN as compared with lignocaine. Pain relief was steady and sustained in those treated with GTN but returned to pre-treatment status within 5 weeks in patients with lignocaine. After 8 weeks of treatment, 80% of patients in Group A showed clinical signs of healing compared to 32% in Group B ($p = 0.001$). Headache was the main side effect of GTN. At 6-month follow-up, recurrence was seen in 3/8 patients in Group B compared to 8/20 in the GTN Group ($p = 1$).

Conclusion: Topical GTN has earlier and a higher rate of clinical healing of anal fissure with acceptable side effects. The recurrence rate is high and comparable to lignocaine ointment. It is a safe and an effective treatment of anal fissure in a South Asian population.

1. Introduction

Anal fissure is a tear in the anoderm that eventually becomes an ulcer. It causes suffering out of proportion to the size of the lesion. Spasm of internal anal sphincter has long been observed in patients with anal fissure and that it leads to high maximum resting anal pressure (MRP).[1] In recent angiographic studies, it was found that the small branches of inferior rectal artery pass through the intermuscular septa of the internal anal sphincter and that the posterior wall of anal canal is less well perfused than the anterior.[2] In this way a high MRP secondary to internal anal sphincter (IAS) spasm compounded by ischaemia of posterior anal commissure leads to increased prevalence and chronicity of anal fissure at the posterior midline of the anal canal.[3]

A search for non-surgical treatment of anal fissure had led to the exploration of novel drugs like glyceryl trinitrate (0.2% GTN),[4] calcium channel blockers, alpha-1 adrenoceptor blockers and botulinum toxin, all with varied success. Most of the studies on the efficacy of GTN for anal fissure are

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from the Western countries. In our country, the current treatment is lignocaine ointment. The effect of GTN on patients from our region remains a knowledge gap. This trial was conducted to compare topical GTN cream with topical lignocaine ointment in the healing of anal fissure and the recurrence rate at 6 months.

2. Patients and methods

A prospective, double blinded, randomised controlled trial was conducted at Jinnah Hospital Lahore, Pakistan, a tertiary referral centre. Approval of the trial was obtained from the local research ethics committee and the project was registered with The College of Physicians and Surgeons of Pakistan. Fifty consecutive consenting patients of all ages and either gender with a documented active anal fissure were recruited in the trial between 2000 and 2001. The diagnosis was entirely clinical. Patients with perianal fistula, perianal abscess, inflammatory bowel disease, haemorrhoidectomy in the preceding year, ischaemic heart disease, migraine and pregnancy were excluded. Anal pain with an anodermal ulcer for less than 8 weeks (and absent sentinel tag) was taken as acute anal fissure, while pain with a non-healing ulcer for more than 8 weeks was taken as chronic anal fissure (regardless of presence or otherwise of the sentinel tag). Patients with previous treatment for the fissure were included if the end of treatment was 3 months before inclusion ('washout period' more than 3 months). The principal author obtained an informed consent in the outpatient department and randomised the patients into two groups (Group A and Group B) (Fig. 1) by choosing a colour-coded card in thick white envelopes. Neither the patient nor the examining consultant was aware of the treatment offered to the particular patient. Group A received 0.2% GTN ointment and Group B received 5% lignocaine ointment (the prevalent treatment for anal fissure at the time). The patients were asked to apply a pea-sized quantity of the given ointment to the anal margin, twice daily for a period of 8 weeks. A 'visual analogue scale for (VAS) pain' scorecard was devised by drawing a straight line between two points taken as 1 and 10. The scale was then equally divided into 10 points. Patients were asked to give 1 point to no pain and 10 points for the worst pain they ever experienced. All patients were advised to keep an accurate record of their pain score daily by using the VAS scorecard. General advice included high fibre and judicious fluid intake with avoidance of straining at defecation. Compliance was determined by subjective enquiry.

Follow-up was arranged at the end of week number 1, 2, 8 and at 6 months. Clinical healing was accepted if two out of three criteria were met from first, self-reported (defecatory) VAS pain score of less than two, second, normal clinical examination (parting the buttocks, effacement of anal verge, digital anorectal exam and anoscopy) and third, epithelialisation or disappearance of the fissure. Clinical signs of healing were assessed by a consultant blinded to the mode intervention.

The primary outcome measure was clinical healing at the 8-week follow-up. The secondary outcome measure was relapse of the fissure at 24 weeks (6 months). It was an intention-to-treat analysis. Patients whose fissures had not healed following treatment with one intervention were offered the other or surgical treatment (examination under anaesthetic, fissurectomy or internal anal sphincterotomy).

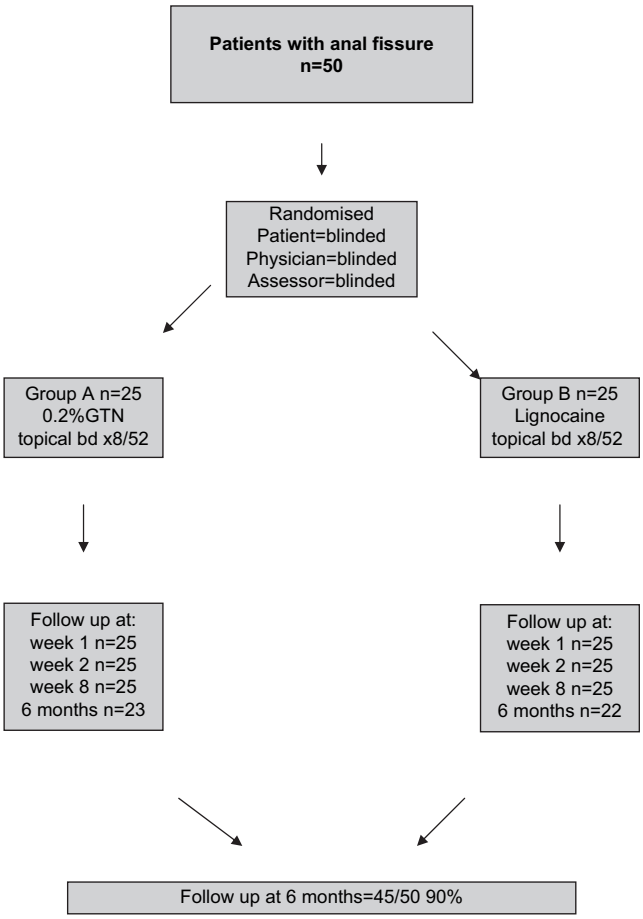

Fig. 1 – Outline of the study.

2.1. *Statistical analysis*

The power was calculated with alpha value of 0.05, beta value of 80% and a difference of 40% in the healing rate. It was based on the expected result of 50% heal rate with lignocaine and 90% with GTN. It calculated 24 patients per treatment arm (total sample = 48). The mean and median with interquartile range (iqr) were calculated. Odds ratio (OR) was calculated for each group. Data were compared using Fisher's exact test. For pain score comparison within the respective group and between Groups A and B, Wilcoxon's signed rank test and the Mann–Whitney *U* test were applied. For all estimations, p-value of <0.05 was considered significant, Microsoft Excel 2000 and SPSS software were used to construct graphs.

3. Results

A total of 50 patients were randomised into two groups, Group A (0.2% GTN, $n = 25$) and Group B (lignocaine, $n = 25$) (Fig. 1). Thirty-two patients were male and 18 female (M:F = 1.7:1).

Table 1 – Demographic details

	Group A (GTN)	Group B (lignocaine)
n	25	25
M:F	1.7:1	1.7:1
Median age	36 years (iqr = 26–42)	33 years (iqr = 22–37)
Acute fissures	9	9
Chronic fissures	16	16
Mean VAS score	5.6	5.04

Table 2 – Effects of the treatment

Outcome	Group A (GTN), $n = 25$	Group B (lignocaine), $n = 25$	*p*-Value
Healing at 8 weeks	20 (80%)	8 (32%)	$p < 0.002$
Side effects			
Headache	17 (68%)	7 (28%)	$p = 0.01$
Pruritis ani	2 (8%)	4 (16%)	Not significant
Postural hypotension	1 (4%)	0	Not significant

Age ranged from nine to 58 years (mean = 31.28, median = 32.5, iqr = 23–37.75). The demographic data at the start of the trial are shown in Table 1. After 8 weeks of treatment, the fissure had healed in 20/25 (80%) patients in Group A (GTN) compared to 8/25 (32%) in Group B (lignocaine) ($p = 0.00144$) (Fig. 2). Symptomatic relief was earlier and sustained in GTN group of patients. Patients who were given lignocaine ointment also showed a subjective improvement initially but their pain scores returned towards the pre-treatment levels by the end of second week. Ninety percent of patients kept an accurate record of their pain scores on the VAS.

The pre-intervention VAS scores in the two groups were comparable ($p = 0.0808$). At 8 weeks post-intervention the GTN group has significant improvement in the VAS scores than the lignocaine group (mean VAS 2.44 for Group A vs. 5.4 for Group B; $p = <0.001$) (Fig. 2).

Significantly more patients in GTN treatment arm complained of headache compared to lignocaine (17 vs. 7; $p = 0.01$) Table 2. It was mild and responded well to paracetamol. None of the participants had to stop the treatment because of the headache. Forty-five patients (90%) were reviewed at 6 months for signs of recurrence. Three out of eight (37.5%) patients in Group B who had healed on lignocaine had a recurrence of anal fissure, compared with eight out of 20 (40%) who had healed following GTN treatment ($p = 1$) (Fig. 3). All recurrences were offered surgical treatment at that point.

4. Discussion

GTN has proved its efficacy in the developed world as a first line treatment for anal fissure. This trial was conducted to evaluate its effectiveness in an entirely different social, economical, cultural and political setting in Pakistan and it confirms that GTN is an effective and a safe treatment for anal fissure.

The staple diet of Pakistanis is rich in fibre and comprises of fresh fruit and vegetables. Obesity, diverticular disease and inflammatory bowel disease are uncommon but constipation remains an everyday problem for the masses.

This study shows a prevalence of anal fissure in males with more patients presenting with chronic anal fissure. This finding partly reflects the social and cultural limitations, as most of the population does not want their pudenda to be examined. The chronicity of the disease reflects the general public attitude as they try alternative therapies before attending a medically qualified doctor. Eighty percent of patients in this trial were successfully treated with GTN as compared to 32% with lignocaine. These figures are comparable with the international studies reporting healing rate of 65–90%.[5,6,9–11] It has been reported that higher doses than 0.2% GTN are not more effective.[7]

VAS for pain was a simple and an effective way to evaluate the subjective improvement of therapy and it was seen that on most occasions the pain scores fell progressively and permanently as the treatment continued with GTN. In some patients on lignocaine treatment, pain was relieved initially, but then returned close to the pre-treatment levels within 5 weeks. These findings were similar to those by Lund as he noted failure of the placebo after 4 weeks.[5] Out of the 17 patients who did not heal in Group B, 12 (71%) showed both subjective and objective signs of improvement with 8 weeks of GTN treatment.

The mean healing time of 4.1 weeks (2–8 weeks) was observed in this study, which is comparable to the results in the West[5] where the healing time was between 2 and 6 weeks.

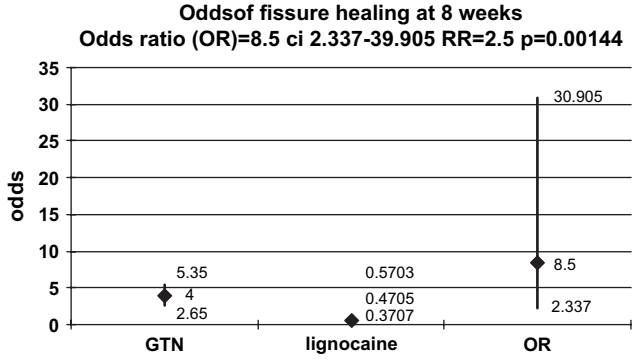

Fig. 2 – Fissure healing at the 8-week follow-up.

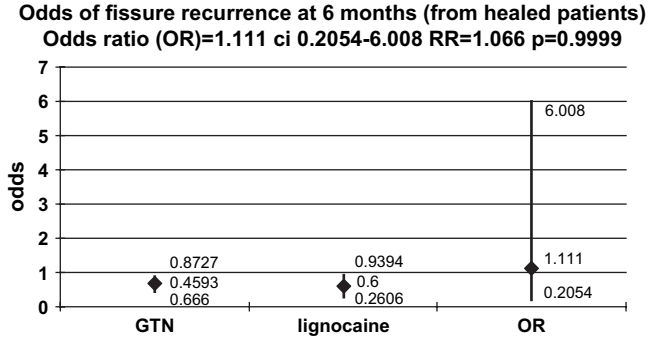

Fig. 3 – Recurrence of fissure at 6-month follow-up.

A recurrence rate of 40% was observed in patients treated with GTN at the 6-month follow-up which is higher than the published international research data.[5,8] This may be due to excessive laxative consumption and poor bowel habit but remains unconfirmed.

Two shortcomings were observed towards the end of the study. First, for isolated assessment of the acute or of chronic fissures, the sample size was not sufficient and preferably should have been considered at the commencement of the trial. Due to the chronicity and the cross scarring of the chronic fissures, selection bias may have resulted.

Second, whereas the assessor at the follow-up was blinded to the type of intervention received, it was preferable if there was a second blinded assessor to counter inter-observer variation as the outcome parameter was being measured subjectively. Nevertheless this trial has yielded clinically beneficial information.

5. Conclusion

In the treatment of a mix of acute and chronic anal fissure patients, topical GTN has a statistically and clinically significant success rate for fissure healing and pain improvement at 8 weeks compared to lignocaine ointment (80% vs. 32%). It came at the cost of clinically acceptable level of morbidity (headache). The relapse rate at 6 months was high at 37–40% and was independent of either treatment modality. The efficacy of GTN for anal fissure in a South Asian population is comparable to that reported in the West.

Conflict of interest
None.

Funding
None.

Ethical approval
Ethical approval was given, by the executive director, Jinnah Hospital Ref: JA-AIMC 5136/00.0x(8)

Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijsu.2007.07.005.

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